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ARTICLE

Adoption Studies of Schizophrenia

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The observation that schizophrenia is more commonly observed among the relatives of individuals with schizophrenia than in the general population does not indicate the mechanism that produces such familiality occurs. Adoption designs permit evaluation of the role of genetic factors in schizophrenia independently of the influence of family environments. Results from studies of adoptees with schizophrenia and their biological and adoptive relatives indicate that genetic factors play a highly significant role in the risk for schizophrenia. This genetically mediated risk to relatives includes an increased prevalence of both schizophrenia and a nonpsychotic syndrome analogous to schizophrenia, but does not represent a general liability to other forms of psychopathology. Although adoption studies have convincingly demonstrated an important role for genetic factors in schizophrenia, the necessity and specificity of such factors, their precise identity, and their interaction with environmental influences remain unknown. Am. J. Med. Genet. (Semin. Med. Genet.) 97:18–22, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Although the tendency for mental illness to occur among the relatives of affected individuals at a greater rate than would be expected by chance has been consistently observed, the cause of this familiality has been variously ascribed to the operation and interaction of both genetic and environmental factors. It is difficult to separate the contribution of these factors in families, because children share both genes and environments with their parents and siblings.

Studies of twins offer one approach to measuring the relative contribution of genetic factors to the liability for schizophrenia. Twins do, however, share their environments from conception, and the similarities of their environments tend to be high for monozygotic and low for dizygotic twins, corresponding with the high and low concordance rates for sz in such pairs, making it difficult to ascribe concordance differences exclusively to genetic variables.

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CRITERIA FOR ADOPTION STUDIES OF SCHIZOPHRENIA

The first report suggesting the use of an adoption study to investigate etiology in schizophrenia [Kety, 1959] noted that with appropriate controls, facilitated by the adoption process itself, separation of genetic from environmental influences could be achieved by studies of adopted individuals and their two families. Such a study might require execution on a national scale to have sufficient power. Although the adoption strategy was originally proposed to disentangle genes from environment in the traditional family study (that could be designated the "adoptees' families" approach), as work toward carrying out such a study progressed, it became clear that there was at least one other approach, that was to study the adopted away children of a parent with schizophrenia (the "high risk adoptees" approach). Kety [1974], Cadoret [1986], Kringlen [1991] and Tienari and Wynne [1994] have previously reviewed the various approaches to adoption studies.

Separation of genetic from environmental influences could be achieved by studies of adopted individuals.

HIGH-RISK ADOPTEES APPROACH

The high-risk adoptees approach studies the adopted-away children of individuals (usually mothers) with schizophrenia. If these children later develop schizophrenia at an elevated rate, their increased risk can be attributed to genetic or perinatal influences from the mother.

One advantage of the high-risk adoptees approach is that it enables investigators to follow the progress of adopted individuals from birth, with the possibility of discerning the earliest signs of illness as they develop. Multiple measurements early in life (prenatal or in infancy) can later be assessed for their

ability to predict illness in adulthood without fear that diagnosis of psychopathology may have biased assessment. A major advantage of the high risk adoptee approach is the ability it confers to study post hoc the effects of different rearing environments.

There are also disadvantages to the high-risk adoptees approach. In particular, the ability to generalize results is limited. A practical concern is that if an investigator wishes to study the early experience of adoptees who later develop schizophrenia, a very long time frame for the study is established. Finally, two potential biases may be operating in the high-risk adoptees approach: 1) to the extent that one is interested in assessing the importance of environmental and genetic factors in schizophrenia, children adopted away from an ill mother may have already experienced negative environmental consequences of their mothers' illness; 2) the placement and subsequent rearing of children of an ill parent for adoption may be biased by knowledge of parental illness.

Despite these concerns, the initial studies of Heston [1966] that found a much greater prevalence of schizophrenia in foster home and institution reared children of mothers with schizophrenia than in the children of controls provided support for the operation of genetic factors in schizophrenia. That support was confounded by the potential for subjective bias in the placement and rearing of the offspring. What Heston's study does very clearly is to remove rearing and other family-specific variables from an influence in the etiology of schizophrenia: half of the high risk offspring were reared by foster parents, the other half were reared in institutions. The prevalence of schizophrenic illness was not significantly different between groups.

A much greater prevalence of schizophrenia in foster home and institution reared children of mothers with schizophrenia.

A similar study was carried out in Denmark by Higgins [1966, 1976] who studied 50 young adults, all born of mothers with schizophrenia, half of whom had been reared by their mothers, the other half, separated from their mothers early in life and reared by agents without a history of mental illness. Four cases of chronic schizophrenia were found in each group and other types of psychopathology were no higher in those reared by their ill mothers. Wender et al. [1974] studied offspring of normal biological parents reared by adoptive parents with severe psychopathology or psychosis. No increased prevalence of schizophrenia spectrum disorders was found among them. One study that avoided the major bias in the Heston and Higgins studies selected the high risk adoptees from a total population of biological parents free of mental illness at the time of adoption, where the onset of schizophrenia in the parents averaged 11 years after the adoption.[Rosenthal et al., 1968]. More recently, a series of reports from Tienari [1991] and his colleagues [Tienari et al., 1994, 1985] have reported significantly higher rates of psychosis among the adopted away children of parents with schizophrenia, and have used a nationwide Finnish sample to explore the interaction between genetic vulnerability and family environment in schizophrenia, including adoptees separated from their biological parents before the onset of parental illness [Wahlberg et al., 1997].

ADOPTEES' FAMILIES APPROACH

The adoptees' families approach begins with a total sample of individuals within the ages of risk for schizophrenia who were adopted at an early age and have since developed schizophrenia. A cohort of case matched controls is selected and the biological and adoptive parents, siblings and half-siblings are identified and screened for mental illness. An excess of schizophrenia observed among members of the biological families of adoptees with schizophrenia is indicative of a genetic contribution to schizophrenia.

An advantage of this approach is that it imposes no requirements for age, gender or fertility on affected subjects, and can thus be more generalized than the high-risk approach. Of particular note is the ability of such studies to examine paternal half-siblings of adoptees, that is, individuals who have the same father, but a different mother, as an identified adoptee with schizophrenia. These paternal half-siblings share only genetic material from their mutual father, and did not share the same womb or perinatal mothering.

One disadvantage of the adoptees' families approach is that large samples are required for meaningful analyses. A second disadvantage is that adoptive parents are demographically different from biological parents, and so appropriate control adoptees and their families must be included in studies. The appropriate comparison is in the prevalence of psychopathology between the biological relatives of ill adoptees and their controls to demonstrate genetic influence and between adoptive relatives to elucidate environmental influences.

The adoptees' families method offers several possibilities to approach the problem of assessing the role of family environment and genetic factors in schizophrenia. In addition to comparing the risk for illness among relatives, it is also possible to assess psychopathology among adoptive parents who raise adoptees who develop schizophrenia to assess whether parental psychopathology seems to contribute to adoptees' illness [Wender et al., 1977]; one can also assess potential effects of assortative mating in half-siblings' coparents [Ingraham and Chan, 1996].

THE DANISH-AMERICAN ADOPTION STUDIES

The advantages of the adoptees' families approach led to its choice as a model on which to conduct a national sample based study of schizophrenia. Working with scientists from Denmark's Kommunehospitalet, index probands were selected from the total register of Dan-

ish adoptees by identifying those adoptees with a history of hospitalization for mental illness and selecting those with evidence from hospital records of schizophrenia. Control adoptees were selected from the pool of adoptees with no history of mental hospitalization to match index adoptees on age, gender, social class of the adopting parents, and time spent with the biological mother. Biological and adoptive relatives of the index and control adoptee probands were identified through adoption court records and population registers, and the national psychiatric register was consulted to identify those relatives who had ever been hospitalized. Subsequently, living relatives were personally interviewed, and diagnoses were made based on the interview and hospital records, if any. Diagnoses were blind and global and based on the characterizations of schizophrenia and latent schizophrenia published by Bleuler [1911]. After interviews of the index and control probands, it became possible to more carefully screen the control probands. To qualify as a control, the putative control probands must have been interviewed and found to be free of significant psychopathology. Methodological details of the Copenhagen and Provincial studies are presented in the original reports [Kety et al. 1968, 1975, 1978, 1994].

Chronic schizophrenia was observed more frequently among the biological relatives of adoptees with schizophrenia.

The first adoptees' family study of schizophrenia [Kety et al., 1968] was conducted in Copenhagen and limited to diagnostic information available in hospital records. Seven years later the same sample was analyzed on the basis of personal psychiatric interviews [Kety et al., 1975]. By 1994 the Copenhagen study had been replicated by the original investigators in the rest of Denmark [Kety et al., 1994] and was independently analyzed using the DSM diagnostic system [Kendler et al., 1994].

Results from the Copenhagen sample of the Danish-American adoption studies revealed that chronic schizophrenia was observed more frequently among the biological relatives of adoptees with schizophrenia (5.6%) than in the biological relatives of control adoptees (0.9%). The non-psychotic schizophrenia-like syndrome of latent schizophrenia was significantly concentrated among the biological relatives of the adoptees with schizophrenia (14.8%), more than twice the prevalence of chronic schizophrenia in these relatives; latent schizophrenia was observed in few (0.9%) of the biological relatives of controls. These results confirmed empirically E. Bleuler's description of a more common, but less severe, schizophrenia-like illness among the relatives of schizophrenia patients, and the adoption methodology used permits the conclusion that the excess of illness seen among biological relatives of adoptees with schizophrenia was due to the influence of genes rather than family environment.

Illness seen among biological relatives of adoptees with schizophrenia was due to the influence of genes rather than family environment.

After the publication of results from the Copenhagen sample of the Danish-American adoption studies, Kety and his colleagues proceeded with a replication in the provinces outside of Copenhagen to test the generality of the original results. The results of the Provincial Sample were similar to the findings of the Copenhagen sample. Chronic schizophrenia was observed more frequently among the biological relatives of adoptees with chronic schizophrenia (4.7%) than in the biological relatives of control adoptees (0.0%). Latent schizophrenia was observed primarily among the biological relatives of adoptees with chronic schizophrenia (8.2% of biological index relatives versus 2.5% in biological control relatives), and again was nearly twice as frequent as chronic schizophrenia. The replication of the original findings in a separate sample provides strong support for the association between latent and chronic schizophrenia; that these results were observed in a blind adoptees' relatives design is evidence that the observed association is mediated through genetic means. That an increase in other forms of psychopathology was not observed among the biological relatives of adoptees with schizophrenia is important; it indicates that the genetic liability among relatives of individuals with schizophrenia is limited to schizophrenia and a closely related syndrome and is not a general liability for psychopathology.

It is possible to pool the results of the two samples to give an overall picture of the risk for schizophrenia and related illnesses in the biological relatives of adoptees with schizophrenia. There is a highly significant concentration of schizophrenia (5.0% vs. 0.4% in controls; Fisher's exact $P = 0.0013$) and latent schizophrenia (10.8% vs. 1.7% in controls; Fisher's exact $P = 0.00002$) among the biological relatives of chronic schizophrenic adoptees.

In addition to the global diagnoses made by the original investigators, interviews from the Copenhagen and Provincial Samples were reviewed and given DSM-III diagnoses by Kendler and his colleagues [Kendler et al., 1981, 1994]. In the national sample, both schizophrenia and schizotypal personality disorder were observed more frequently in relatives of adoptees with schizophrenia than in relatives of controls.

DISCUSSION

Adoption studies of schizophrenia have established and confirmed the significant role of genetic factors in the etiology of this disorder. That a similar risk for schizophrenia among biological relatives is observed across a number of adoption and family studies [Gottes-

man, 1991; Kendler and Gardner, 1997] suggests that whatever environmental factors are operating in schizophrenia, they are equally present in the adoptive and non-adoptive families of individuals who develop schizophrenia. Future studies of schizophrenia related syndromes [Ingraham, 1999] and specific features of psychopathology in schizophrenia [Kinney et al., 1997] will continue to benefit from the clear separation of environmental and genetic factors that adoption studies offer.

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Investigation of the etiology of schizophrenia has been hampered by variability in definitions of the disorder. Schizophrenia remains a syndrome, not a disease, and the validity of diagnostic criteria are not ensured by their reliability. Comparison between the global diagnostic system used by Kety et al. [1994] and DSM criteria [Kendler et al., 1994] suggests that the global approach can result in higher sensitivity with comparable specificity in diagnoses characterizing the relatives of individuals with schizophrenia.

Knowledge of genetic relatedness of putative syndromes would do much to clarify diagnosis and classification. The process of establishing valid boundaries of the syndrome of schizophrenia can be advanced through adoption studies that seek to identify syndromes associated with shared genetic material, but not shared family environments [Ingraham, 1995]. At the time of the initial Danish-American adoption studies, adoptees with acute schizophrenia, reflecting a non-chronic, resolving psychosis potentially related to schizophrenia, were evaluated in addition to adoptees with chronic schizophrenia. The absence of affected relatives of acute schizophrenia probands was evidence that empirically narrowed the syndrome of schizophrenia. Conversely, the observation of increased risk for the less severe syndrome of latent schizophrenia among relatives of probands with chronic schizophrenia broadened the genetically influenced schizophrenia spectrum of psychopathology to include a non-psychotic syndrome. Further analysis [Kendler et al., 1994] of the risk of schizotypal personality disorder (SPD; the DSM diagnosis that is analogous to latent schizophrenia) in the relatives of adoptee probands diagnosed with either schizophrenia or SPD indicated a higher risk for SPD among the biological relatives of probands with SPD, suggesting that genetic vulnerability for schizotypal traits may in part be transmitted independently of the risk for schizophrenia.

A potential weakness of existing adoption studies of schizophrenia has been their focus on a single form of psychosis, as there are multiple illnesses that can have psychotic features. Even though interviewers and raters have been blind to individuals' status as adoptive or biological relatives and to the presence or not of illness among relatives, raters have not been blind to the form of psychopathology of interest. A rater knowing that a study is focusing on schizophrenia may be biased toward identifying symptoms consistent with schizophrenia, or may consider any psychotic feature to be schizophrenia-related. Future studies can avoid this potential confound by including probands with bipolar illness and major affective disorder. This strategy will also have the advantage of being able to clarify genetic links, if any, among the major psychoses.

Adoption studies have convincingly demonstrated a significant role for genetic factors in schizophrenia. As compelling as the results may be, the necessity and specificity of such factors, their precise identity, and their interaction with environmental effects remain unknown. The establishment of a genetic factor in schizophrenia in no way rules out the operation of environmental factors, nor does it specify when during development, where in the body, or how such factors operate. Despite our current ignorance of the mechanisms affected by genes related to schizophrenia, we can proceed with confidence that there are such genes to be found.

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